

REMARKS/ARGUMENTS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Upon entry of this Amendment, claims 23 to 25 and 27 to 33 will be pending in this application. Entry of this Amendment After Final Rejection is believed to place the application in a condition for allowance, or simplify the issues on appeal. Accordingly, entry of this amendment is respectfully requested.

The claims stand rejected under 35 U.S.C. §112, first paragraph because the specification fails to provide a sufficient written description or an enabling disclosure. The Applicants respectfully submit that the claims are allowable under §112 in light of the above amendments and for at least the following reasons.

The Examiner contends that the specification fails to provide enablement for a method using any TSH receptor antibodies or any selective antibody against the human TSH receptor, and a suitable written description regarding this method. The applicants submit that the specification fully describes the conformational monoclonal antibodies of the present invention. The production of monoclonal antibodies raised against several forms, including fragments and non-functional forms, of TSH receptors (human or other) in different species is amply described in the relevant scientific literature (*See* the specification at pages 24-25).

Any such antibodies can be screened using the method described in sections 1.4.4.1 and 1.4.4.2 by using a panel of short synthetic peptides spanning the whole length of the known sequence of the human TSHR. Table 1 shows the epitopes to which a binding of the examined monoclonal antibodies was observed. All antibodies except antibodies 9, 10 and 11 showed binding to some of the peptides and, therefore, were “sequential” antibodies. Antibodies 9, 10 and 11 of table 1 – although they were the most effective ones in precipitating rhRSHR/TSH complexes and, therefore, showed strong binding to the rhTSHR – did not bind to any of the synthetic peptides corresponding to short partial sequences of the hTSHR.

The preparation of suitable conformational anti-TSHR antibodies by genetic immunization is fully described in the specification by the cited reference on page 31, S. Costagliola and G. Vassart, *J. Endocrinol. Invest.*, 20 (Suppl. 2, No. 5.) (1997). Thus, the skilled artisan would be able to prepare the conformational antibodies in question without

undue experimentation. Accordingly, withdrawal of these rejections is respectfully requested.

The claims stand rejected under 35 U.S.C. §103(a) as unpatentable over Vitti *et al.* (*Acta. Med. Austriaca.*, 23(1-2):52-6, 1996) or US 5,614,363, each in view of Harlow *et al.* (*in Antibodies A laboratory Manual, Cold Spring Harbor Laboratory*, 1988, pp. 556, 564-91), Nicholson *et al.* (*J Mol Endocrinol.*, 16(2): 159-70, 1996), and/or Morgenthaler *et al.* (*J. Clin. Endocrinol. Metab.*, 81(2): 700-6, 1996). Additionally, the claims stand rejected as obvious over US 5,814,461 ('461), in view of US 5,614,363 Harlow *et al.*, Nicholson *et al.*, or Morgenthaler *et al.* The Applicants respectfully traverse these rejections for at least the following reasons.

The Applicants maintain that the present invention is non-obvious over the cited references for all the reasons of record. Despite noting that prior attempts to immobilize TSH receptors *met with failure* (See US 5,814,461, Col. 2, lines 64-57), the Examiner nonetheless considers the immobilization of these receptors obvious. Even if this were true, nothing in the primary references, whether or not combined with the secondary references, teaches the immobilization of a recombinant human TSH receptor to a solid support by a selective monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor.

Accordingly, withdrawal of these rejections is respectfully requested.

Therefore, all objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Should any issues remain unresolved, the Examiner is encouraged to contact the undersigned attorney for Applicants at the telephone number indicated below in order to expeditiously resolve any remaining issues.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: 

Christopher M. Beck
Registration No. 52,603
Direct No. (703) 905-2013

Paul L. Sharer
Registration No. 36,004
Direct No. (703) 905-2180

PLS/CMB
1600 Tysons Boulevard
McLean, VA 22101
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Date: February 2, 2004